Case Reports

Long-standing Angioedema With C1 Esterase Inhibitor Deficiency Associated With Occult Lymphoma

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ACQUIRED DEFICIENCY of the C1 esterase inhibitor protein, which produces a clinical picture closely resembling hereditary angioedema, was first described in a patient with lymphoma by Caldwell and co-workers[1] in 1972. A recent review stressed the importance of differentiating the hereditary and acquired forms of C1 esterase inhibitor deficiency in view of the fact that many patients with the acquired type have underlying lymphoproliferative disease. Other causes include a number of diseases with autoimmune features.[2] In one patient acquired C1 esterase inhibitor deficiency was presumably related to an adenocarcinoma of the rectum.[3] We recently observed acquired C1 esterase inhibitor deficiency in a 43-year-old man with a remarkably long history (six years) of recurrent angioedema who was otherwise asymptomatic. Further evaluation led to the discovery of a non-Hodgkin's lymphoma that may have been indolent during the entire period of his illness. His case is noteworthy for the unusually long prodrome of intermittent angioedema before the diagnosis of lymphoma and further underscores the necessity to distinguish the acquired and hereditary conditions so that specific therapy for the underlying cause of the acquired form may be considered.

Report of a Case

A 43-year-old male minister was referred to Stanford University Hospital in November 1979 for recurrent episodes of angioedema. The attacks had begun in 1974 shortly after a cholecystectomy for gallstones. A presumptive diagnosis of hereditary angioedema had been made in November 1978, based on a C1 esterase inhibitor level of <4 mg per dl (normal 8 to 30 mg per dl). He described attacks of nonpitting edema involving one or several extremities, which resolved completely within four days. He consistently noted malaise and arthralgia for several days before each episode. He said there was no relationship of his symptoms to physical trauma or dental procedures, but considered emotional stress to be a definite precipitating factor. Brief trials of indomethacin and diphenhydramine hydrochloride therapy in 1977 had no effect on his symptoms. Beginning in April 1978, an additional prodrome of crampy abdominal pain and diarrhea developed, which usually resolved after the appearance of extremity swelling. He also had frequent attacks of pharyngeal edema, but these did not result in airway obstruction.

During 1978 the episodes had increased in frequency and at the time of his first Stanford visit were occurring every 10 to 14 days. He said he had neither fever nor weight loss but had had night sweats dating back to 1974. For the past two years he had noted the appearance of asymptomatic papular and nodular lesions on his chest, back and thighs. His past medical history was unremarkable with the exception of a cholecystectomy in 1974, a vasectomy in 1973 and a tonsillectomy in 1958. There was no family history of angioedema, lymphoproliferative or autoimmune disease.

On physical examination numerous bulging, flesh-colored lesions 0.5 to 2.5 cm in diameter were scattered over his shoulders, chest and thighs. Bilateral 1 by 2 cm posterior cervical and left supraclavicular nodes were noted without other lymphadenopathy. There was no extremity or pharyngeal edema. The liver and spleen were not enlarged. No abdominal masses were palpable. The physical examination otherwise showed no abnormalities.

Laboratory evaluation included a C1 esterase inhibitor level by radial immunodiffusion of <4 mg per dl (normal 14 to 30, Scripps Immunology Reference Laboratory, La Jolla, Calif.). Serum C4 was undetectable, C3 was 137 mg per dl (normal 90 to 120) and C1q was <4 mg per dl (normal 14 to 20). All of the above assays were done by radial immunodiffusion. The hemoglobin level was 14.6 grams per dl and total leukocyte count was 6,800 per cu mm, with 53 percent granulocytes, 39 percent lymphocytes, 5 percent monocytes and 2 percent eosinophils. The peripheral blood lymphocyte morphology appeared normal. Urine analysis and tests for erythrocyte sedimentation rate, serum electrolytes, blood urea nitrogen, creatinine, serum aspartate aminotransferase (formerly SGOT), lactic dehydrogenase and alkaline phosphatase gave values within normal limits. The fluorescent antinuclear antibody test was weakly positive (1:80) with a diffuse pattern. The latex fixation test was negative. Serum immunoelectrophoresis showed a monoclonal IgM of *k*-light chain

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type. Free *k*-light chains were detected in a concentrated urine specimen by immunoelectrophoresis. The quantitative immunoglobulins showed IgM of 771 mg per dl (normal 60 to 280), IgG of 535 mg per dl (normal 800 to 1,800) and IgA of 42 mg per dl (normal 90 to 450).

A biopsy of the left supraclavicular lymph node was done. The nodal architecture was overrun by a vaguely nodular proliferation of small lymphoid cells. These appeared to represent an admixture of normal-appearing lymphocytes and slightly larger cells with angulated, irregular nuclear membranes. Germinal centerlike structures were also seen. This was considered to represent lymphocytic lymphoma of intermediate differentiation* as recently defined by Mann and associates.[4] The bone marrow biopsy specimen showed several lymphoid nodules, some of which were paratrabecular in location and some of which were large and composed of round lymphocytes. Biopsy specimens from the soft papular skin lesions showed a loss of elastic tissue of the dermis and moderate perivascular lymphohistiocytic infiltrates that were not considered to represent lymphoma.

Liver-spleen scan showed enlargement of both organs without focal defects. Massive para-aortic and iliac adenopathy was seen on lymphangiography.

Because his episodes of angioedema were frequent and disabling, administration of danazol (600 mg a day) was begun in December 1979 and continued to the present. He had no further attacks of abdominal pain or angioedema. The C4 and C1 esterase inhibitor levels remained extremely depressed at one and three months after the start of treatment. Because of extensive retroperitoneal lymphadenopathy, treatment for his lymphoma was recommended. He declined chemotherapy and chose to participate in a protocol using fractionated low-dose total body irradiation as a single modality. He was treated with 15 rads of total body irradiation twice a week to a total dose of 150 rads. This therapy was well tolerated and for several months serial abdominal x-rays showed significant reduction of the massive pelvic and para-aortic nodes. However, because of increasing lymphadenopathy combination chemotherapy was begun in March 1981.

Comment

Patients with either hereditary or acquired C1 esterase inhibitor deficiency have recurrent episodes of nonpitting edema involving the extremities, face, airway and gastrointestinal tract. Low serum levels of the C1 esterase inhibitor and C4 are features of both conditions and thus these tests are of little help in differential diagnosis. Whereas the onset of symptoms in mid to late life favors the acquired condition, in a few patients who have hereditary angioedema symptoms first develop after the fourth decade. The two disorders can be readily distinguished by measurement of the C1q level because in the acquired deficiency the C1q is profoundly depressed, whereas in hereditary angioedema the level is normal or only minimally depressed.[2] The laboratory findings in our patient (decreased C1 esterase inhibitor, C4, C1q and the presence of monoclonal IgM) resemble those previously reported in patients with acquired C1 esterase inhibitor deficiency associated with lymphoproliferative disease.[2] His unusually long history of recurrent angioedema, however, was a point that argued against the presence of an underlying malignancy. In the previous reports of acquired C1 esterase inhibitor deficiency and lymphoma, angioedema developed within months of the diagnosis of lymphoma.[5,6]

Whereas danazol administration is effective prophylaxis for the attacks of hereditary angioedema, other published articles contain little information on its ability to prevent the episodes of angioedema in acquired C1 inhibitor deficiency due to lymphoma. In one patient who had asymptomatic C1 esterase inhibitor deficiency and lymphoma, the C1 inhibitor level rose to normal after 23 days of treatment with full doses of danazol; the C1, C4 and C2 levels, however, remained low.[7] In the one patient with rectal carcinoma and C1 esterase inhibitor deficiency, danazol administration led to resolution of angioedema attacks and normalization of the C1 esterase inhibitor and complement levels.[3] These levels subsequently fell without evidence of tumor recurrence. In our patient the institution of danazol treatment eliminated the attacks of angioedema but had no measurable effect on C1 esterase inhibitor, C4 or C1q levels. The drug presumably led to increased synthesis of the C1 esterase inhibitor[8] and the establishment of a state of compensated consumption of the inhibitor protein. In four previously reported cases (including one with lymphoma), treatment of the underlying disease led to resolution of the episodes.[2] In the present case the C1 esterase inhibitor and C4 levels remained greatly depressed despite a partial clinical response of the lymphoma to radiotherapy; on danazol therapy he remained free of angioedema, however. It will be of interest to follow the effect of combination chemotherapy on the levels of C1 esterase inhibitor, C4 and circulating paraprotein.

Acquired C1 esterase inhibitor deficiency may be more common than previously recognized. The differentiation of this disorder from hereditary angioedema is important for diagnosis, prognosis, therapy and genetic counseling. The lack of a family history does not necessarily indicate the acquired form since in one series of patients who had hereditary angioedema a fourth were unaware of a family association.[9] In most of these cases, studies of asymptomatic first-degree relatives showed the hereditary nature of the defect. Acquired C1 esterase inhibitor deficiency should be an early consideration in the evaluation of hereditary angioedema-like syndrome with a negative family history. In this setting, noninvasive screening for illnesses known to be associated with acquired C1 esterase inhibitor deficiency and measurement of the C1q level are indicated. A normal C1q level would point to hereditary angioedema, and subsequent measurement of the C1 esterase inhibitor level in first-degree relatives would confirm this diagnosis in most instances. Signifi-

*Lymph node material was reviewed by Dr Ronald Dorfman.

cant depression of the C1q level should prompt further evaluation for lymphoma and other conditions associated with the acquired inhibitor deficiency.

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Fulminant Neonatal Hepatic Necrosis Associated With Echovirus Type 11 Infection

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NEONATAL HEPATIC NECROSIS is fortunately rare.[1] Although a variety of enteroviruses have been recognized to infect fetuses and neonates,[2-4] the cause of most cases of fulminant neonatal hepatic necrosis is unknown.[1] Occasionally cytomegalovirus,[5] rubella[6] and echovirus types 3,[7] 6,[8] 9,[9] 11,[8,10,11] 14[12] and 19[13] have been directly associated with fatal hepatic necrosis during the neonatal period.

We report four cases of neonatal hepatic necrosis associated with echovirus type 11. These cases occurred sporadically during one year and each patient came from a different geographic area; thus at no time was an epidemic of echovirus type 11 suspected.

The perinatal histories were negative for viral illness as manifested by fever, vomiting, diarrhea or upper respiratory tract infections.

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Postmortem studies in case 4 were done by Zrino Bezmalinovic, MD.

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TABLE 1.—*Summary of Clinical Features and Results of Laboratory Investigations*

Data	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Birth weight (grams)	3,856	3,359	3,154	2,765
Admission weight (grams) .	3,000	2,934	3,000	2,540
Gestation (weeks)	37	38	38	38
First symptoms	Jaundice	Jaundice	Jaundice	Jaundice
Age	5 days	6 days	6 days	5 days
Bilirubin (mg/dl)				
(normal 1-12)	10.1	10.3	11.3	14.1
Platelet count (per cu mm)	39,000	46,000	10,000	31,000
Fibrinogen (mg/dl)				
(normal 200-300)	...	12	40	40
Fibrin-split products (μg/dl)				
(normal 0-3)	40	40	40	40
AST (IU) (normal 11-40)*	5,530	7,480	1,182	1,029
ALT (IU) (normal 11-40)†	1,370	2,040	227	197
AST/ALT ratio	4.0	3.6	5.2	5.2
Prothrombin time (sec) ...	45.0	33.5	28.9	28.6
Blood ammonia (μg/dl)				
(normal 11-35)	NP	158	108	NP
Viral cultures (Echovirus II)				
Liver	+	+	+	+
Lung	+	+	+	+
Parents	NP	NP	NP	NP

NP = not performed; + = positive.

*Aspartate aminotransferase, formerly SGOT.
†Alanine aminotransferase, formerly SGPT.

Reports of Cases

CASE 1. This infant was delivered by cesarean section to a 26-year-old primigravid woman. The mother was treated throughout her pregnancy with phenytoin sodium and phenobarbital for the control of a seizure disorder. Birth weight was 3,856 grams. The infant was discharged home at 3 days of age after an unremarkable hospital course.

The parents noted that the infant at 5 days of age was jaundiced, lethargic and had mottling of the lower extremities; he was readmitted to hospital. Examination showed that the abdomen was distended and tender with the liver edge palpable 8 cm below the right costal margin. Pertinent laboratory data are summarized in Table 1. Despite exchange transfusion with packed cells reconstituted with fresh frozen plasma, the infant's condition steadily deteriorated until his death the next day. The parents and a 15-month-old sibling were asymptomatic throughout the neonate's illness.

CASE 2. This infant was delivered by cesarean section because of cephalopelvic disproportion. The perinatal history was unremarkable except for a vaginal yeast infection two weeks before delivery. The Apgar score was listed as 9 at one and at five minutes. Birth weight was 3,359 grams. The infant had an unremarkable hospital course and was discharged home on the third day.

On the sixth day of life, a temperature of 39°C (102°F) developed and he was found to be jaundiced, with a serum bilirubin level of 10.7 mg per dl. A workup for sepsis was done, including a lumbar puncture, but proved negative. He became more lethargic and jaundiced and had some respiratory distress. The liver